Contains Nonbinding Recommendations

Draft Guidance on Duloxetine Hydrochloride

Active ingredient: Duloxetine Hydrochloride

Form/Route: Delayed Release Pellets Capsule/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 60 mg base
   Subjects: Healthy males and nonpregnant females, general population
   Additional Comments: Due to the need to maintain the enteric coating, the subjects in a BE study should be advised not to crush or chew the enteric coated pellets.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: EQ 60 mg base
   Subjects: Healthy males and nonpregnant females, general population
   Additional comments: Please see above.

Analytes to measure (in appropriate biological fluid): Duloxetine in plasma

Bioequivalence based on (90% CI): Duloxetine

Waiver request of in vivo testing: EQ 20 mg base, EQ 30 mg base based on (i) acceptable bioequivalence studies on the EQ 60 mg base strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in vivo testing.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

In vitro alcohol dose dumping testing
Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 1000 mL, 0.1 N HCl, USP apparatus I (basket) at 100 rpm, with or without the alcohol:

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours

Please submit standard operating procedures (SOPs) for the testing method, individual dissolution data of Duloxetine, percent of breakdown products (1-naphthol, and 1,4-rearrangement compound) at each time point, mean values, standard deviations, coefficient of variation (%CV), and plots of the percent release profiles of duloxetine, 1-naphthol, and 1,4-rearrangement compound over the 2-hour period.

In vitro 6 hours stability testing
Due to concerns that some patients may have delayed gastric empting time that may lead to the release of duloxetine in the stomach, which may lead to the formation of 1-naphthol, the DBE requests that you conduct comparative in vitro stability testing on all strengths of the test and RLD products (12 units each) using the following method:

Testing Method: 0.1 N HCl, 1000 mL (without alcohol), USP apparatus I (basket) at 100 rpm, for 6 hours.

Please submit standard operating procedures (SOPs) for the testing method, individual dissolution data for Duloxetine, percent of breakdown products (1-naphthol, and 1,4-rearrangement compound) at each time point, mean values, standard deviations, coefficient of variation (%CV), and plots of the percent release profiles of duloxetine, 1-naphthol, and 1,4-rearrangement compound over the 6-hour period.